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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,294	02/02/2004	Andrew D. Miller	YOUZ 2 00059-2	1414

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/770,294	Applicant(s) MILLER ET AL.	
	Examiner Vanessa L. Ford	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 March 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *31 March 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *23-70*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Advisory action.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Advisory Action.

Advisory Attachment

1. This Office Action is responsive to Applicant's amendments and responses filed March 31, 2006. Claims 1-22 are cancelled. Claims 23-70 are under examination. Applicant's submission of the declaration filed under 37 C.F.R. 1.131 by Dr. Keller along with Exhibit A is acknowledged. Applicant's submission of Exhibits 1-4 are also acknowledged. It should be noted that the rejection under 112, first paragraph is maintained for claims 23-70 in the Final Office action. The Examiner address/stresses this point because a typographical error made and it was unclear as to what claims were being maintained

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejection Maintained

3. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 23-70 for the reasons set forth on pages 3-6, paragraph 4 of the Final Office Action.

The rejection was on the grounds that the claims are directed to a method for treating a genetic disorder or condition or disease in a patient in need of treatment comprising administering an effective amount of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine; further wherein two or more of the amine groups of the polyamine are separated by an ethylene group.

The claims broadly encompasses gene therapy, wherein the claimed method of treating a genetic disorder or condition or disease, is treated by administering a cationic lipid compound admixed with or associated with a nucleotide sequence.

The specification teaches that the compound of the invention is used in gene therapy, especially gene transfer (page 1). The specification teaches that one aspect of gene therapy involves the introduction of foreign nucleic acid into cells so that it is expressed protein may carry out a desired therapeutic function (page 1). The specification teaches that this type of therapy includes the insertion of TK, TSG or ILG gene to treat cancer, the insertion of the CFTR gene to treat cystic fibrosis, the insertion of the NGF, TH or LDL genes to treat neurodegenerative and cardiovascular disorders, the insertion of the IL-1 antagonist gene to treat rheumatoid arthritis, the insertion of the HIV antigens and the TK genes to treat AIDS and CMV infections, the insertion of antigens and cytokines to act as vaccines and the insertion of β-globin to treat haemoglobinopathic conditions such as thalassaemias (page 1). There are no working examples in the instant specification to guide the skilled artisan in practicing the claimed method.

The state of the art for gene therapy as discussed by Vile et al *(Gene Therapy, Vol. 7, pp. 2-8, 2000)* is unpredictable. Vile et al teach that the problems in which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. Vile et al teach that there is already a battery of genes that we know are very effective in killing cells and if these genes can be expressed at the right site and at appropriate levels therapy may be occur (page 2). However, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Vile et al teach that whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column) and the requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column). Vile et al teach that a genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. Vile et al teach that in truth, no such systemically targeted vectors exist yet. Vile et al teach that injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column). In addition, Rochlitz C. F. *(Swiss Medicine Weekly, 131:4-9, 2001)* teaches that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach (gene therapy) in any human disease. Rochilitz teaches that although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (see page 8, bottom of page). Rochlitz teaches that the main problems are still the lack of vectors with high transduction efficiency *in vivo*, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology" (pages 8-9).

Thus, as taught above the state of the art regarding gene therapy is considered highly unpredictable. Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (e.g. intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a therapeutic response using a recombinant virus, lentivirus, adenovirus, retrovirus or bacterium comprising the nucleic acid encoding the antigen. The state of the art regarding the route of administration for gene therapy as exemplified by Verma et al, (*Nature, Vol. 389, No. 6648, pages 239-242, 1997)*, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. .Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating a genetic disorder, or condition or disease in a patient.

Applicant's Arguments

A) Applicant's assert that undue experimentation is not required to practice the claimed invention. Applicant urges that the instant specification is replete with working examples. Applicant urges that the specification discloses both in vitro and in vivo testing using cationic liposomes for gene delivery.

Applicant urges that the specification as filed includes an enabling disclosure of a method for treating a genetic disorder or condition or disease in a patient. Applicant refers to pages 18, 19, and 24 and Figure 25 of the instant specification to support their position.

B) Applicant urges that at the time the invention was made it was known in the art to use reporter gene assays to assess therapeutic potential. Applicant refers to Alton et al, 2000 to teach that cystic fibrosis reporter genes can be used in *in vivo* studies. Applicant urges that Dorin et al, 1996 teach that "modest levels of transgene expression and only partial correction of CFTR channel activity may have significant clinical impact". Applicant urges that: (1) the application includes numerous working examples, including in vivo testing, (2) the in vivo testing in the specification measures gene delivery by CAT expression, (3) at the application was filed, CAT expression was also known as a way to evaluate therapeutic potential and (4) at the time the in invention was filed, it was known in the art that a relatively small amount of gene expression in a cell could have significant clinical impact and provide therapeutic relief for conditions such as cystic fibrosis .

C) Applicant urges that mice are an acceptable model for cystic fibrosis. Applicant refers to Boyd et al, 2004 and Hoffman et al, 2005.

D) Applicant urges that the declaration submitted by Dr. Keller demonstrates that a person skilled in the art could based on the present application readily ascertain the transfection ability of liposomes/nucleic acid complexes without undue experimentation.

Examiner's Response to Applicant

Applicant's arguments filed March 31, 2006 have been fully considered but they are not persuasive.

It is the Examiner's position that the specification is not enabled for the claimed method.

A) To address Applicant's comments regarding page 19 and figures 24 and 25, it should be noted that the figure 24 relates to *in vitro* data as a result of studies performed using cystic fibrosis epithelial cells. Figure 25 of the instant specification recites that the *in vivo* data was obtained by the intranasal instillation of cationic liposome/plasmid DNA complexes in to the lungs of female BALB/c mice. Thus, the instant specification teaches the delivery of cationic liposomes to the lungs of BALB/c mice. This assay determines gene delivery activity and not treatment of cystic fibrosis or any other genetic disorder, condition or disease (see page 16 of the instant specification). The instant specification does not include information on how the cationic liposomes were used to treat mice with cystic fibrosis or any other genetic disorder, condition or disease. Therefore, the instant specification is not enabled for treating a genetic disorder, condition or disease in a patient.

B) To address Applicant's comment regarding the knowledge of the art at the time of filing, it must be remembered that Applicant must be enabled for the claimed invention at the time of filing. It must also be remembered the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods. Thus, Applicant must provide evidence which is reasonably predictive that the claimed methods are effective for treating a genetic disorder, or condition or disease in a patient. Dorin et al merely demonstrates that there is a relationship between Cftr gene expression, chloride ion transport and survival are non linear (page 798, first column). Alton et al merely demonstrates that gene expression is greater and lasts longer in adult mice compared with your mice *in vivo.* This article merely suggests that cationic vectors may have implications in the design of future gene therapy trials.

C) The Examiner agrees with Applicant's comments that the mouse can be used as an animal model for cystic fibrosis since Applicant's cited art (e.g. Boyd et al and Hoffman et al) suggest that mice can be used as acceptable animal model for cystic fibrosis. However, the instant specification has not disclosed a method of treating a genetic disorder or condition by administering to a subject (e.g. a mouse) an effect amount of a compound comprising a cholesterol group or derivative thereof having

linked thereto a head groups. The specification merely discloses that mice are administered cationic liposomes/plasmid DNA in gene delivery assays. See pages 24-27 of the instant specification. There is no indication as to what genetic condition or disorder the mice used in the gene delivery assays were suffering from. Thus, there was no indication that a genetic disorder or condition was being treated. The specification has failed to teach or disclose the claimed method.

D) The declaration submitted by Dr. Keller under 37 CFR 1.132 filed 3/31/06 is insufficient to overcome the rejection of claims 23-70 under 35 U.S.C. 112, first paragraph as set forth in the last Office action; the declaration does not provide evidence that the administration of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group can be used to treat genetic disorders or conditions in subjects that are in need of such treatments.

To address the declaration submitted by Dr. Keller, it should be noted that the declaration merely discloses that reporter gene assays may be used to assess therapeutic potential by measuring CAT expression at the time the invention was made. It should be remembered that the claimed invention is directed to method of treating a genetic disorder or disease. There is no evidence (via working examples) in the instant specification or the cited art from Applicant that demonstrates the administration of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine, further wherein two or

more of the amine groups of the polyamine group are separated by an ethylene group to a patient in need of treatment for a genetic disease or disorder which results in the treatment of said patient against the genetic disorder or condition. The cited art merely disclose the transfection ability of liposome/plasmid DNA compounds and suggest that they may have therapeutic potential.

In view of all of the above, the rejection under 112, first paragraph is maintained.

Conclusion

4. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272–1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (571) 272-8300.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
June 1, 2006

NITA MINNIFIELD
PRIMARY EXAMINER